THE PHYSIOLOGICAL ACTION OF HEMLOCK AND ITS ALKALOID.

BY B. F. LAUTENBACH, M.D.

The ancient Greek physicians possessed a more accurate knowledge of the physiological effects of conium than was acquired by more modern investigators until a comparatively recent period. So late as the year 1845, a well-ascertained and carefully observed case of poisoning by hemlock disclosed truths respecting its toxical action which had laid dormant for centuries. An occasional ray of light has indeed appeared to those who from time to time have sought to determine the properties of the plant: but the general state of our knowledge may be summed up in the words of a very eminent therapeutist. About sixteen years ago Pareira (Elem. Mat. Med., vii.) wrote: "In the present state of uncertainty with respect to the real physiological operation of hemlock, it is obviously impossible to lay down indications or contra-indications for its use which can be much relied on."

Since these words were written a number of investigators have appeared in the field, the majority of whom have been content with studying the most marked symptom of hemlock-poisoning, *i. e.*, paralysis, while a few announced idle theories in regard to its action, which others have again disproved. Reference to the most modern treatises on therapeutics shows that very little, apart from its bare toxical effects, is known of its physiological operation, and the little that is known is involved in such a mass of contradictory evidence as to have led some authorities to ignore it altogether.

As conia represents the entire active principle of hemlock, I shall confine my observations almost exclusively to it.

In man the chief symptom produced, when conia is taken in doses just sufficient to decidedly impress the system, is great muscular weakness; this is accompanied by giddiness, and occasionally by disorder of vision. There is an intense desire to lie quiet in a semi-horizontal position, and owing to the heaviness of the eyelids which now occurs, the eyes are kept shut, thus giving rise to the impression that the person is asleep. On attempting to walk the subject's feet feel as though they did not belong to him, and he falls from his knees refusing him support. The pulse is at

first increased and afterwards decreased in frequency. Sooner or later, as the drug impresses the system, the pupils dilate. In some persons these symptoms are accompanied, rarely preceded, by symptoms of gastro-intestinal irritation, nausea, and rarely vomiting. If the dose be a poisonous one, we have, in addition to these symptons, total failure of voluntary motion and convulsive movements occurring (vide a case of poisoning by hemlock leaves reported by Dr. Bennett in Edin. Med. and Surg. Journ. for 1845).

A close physiological study of conia can best be made by investigating its effects on the different systems, seriatim, and this method I shall endeavor to follow.

Physiological Effects on Vegetables.

Worcet (Amer. Chem. et Phys. xxix. 21, 9) placed a haricot plant (Phaseolus vulgaris) in a solution of five grains of the extract of hemlock; in a few minutes the two lower leaves curled at their extremities; the next day they were yellow and subsequently died. The experiments of Schübler and Zeller (Schweiger's Journ. f. d. Chem. B. 1, S. 54) confirm this poisonous action of the extract. The same results were obtained in several experiments made by the writer.

Exp. 1. 11.55 A. M., placed two plants (Ailánthus glandulosus) of equal age, growth, etc., in separate bottles; bottle number one containing a seven-grain solution of extract of hemlock, while bottle number two contained an equal quantity of pure water. 3.05 P. M., the plant placed in bottle number two is in as good condition as when first placed there, while the plant in bottle number one is drooping. 5.30 P. M., the lower leaves of the plant in the hemlock solution are curled at their extremities, while the plant in water is still in an excellent condition. 9.30 P. M., the plant in water is still unchanged, but the lower leaves of the other plant are more curled than before, while the upper leaves and branches hang down the sides of the bottle. The next day at 6. A. M. the lower leaves of the plant in the hemlock solution were dry and brittle, while the other plant remains unchanged. On the third day at 10.30 P. M., the entire plant which was in the hemlock solution was dry and brittle, while the plant which was placed in water had undergone little or no change.

Exps. 2 and 3 gave identical results.

That this poisonous action of the extract of hemlock is due to impurities and not to the exceedingly small quantity of conia which it contains, was shown by the following experiment:—

Exp. 4. Placed two young ailanthus plants in bottles, one bottle containing a one-grain solution of conia, and the other containing pure water. In three and a half days the plant placed in water drooped, and on the fifth day it was dry and brittle, while the plant placed in the conia solution did not droop until the eighth day.

This experiment, taken in connection with another which gave similar results, proves that conia, instead of acting injuriously on plants, really preserves them from decay. As the alkaloid had to be dissolved in a small amount of alcohol, the thought suggested itself that the preservative action was due to the alcohol; but, in the experiments made by the writer to determine this point, it was ascertained that alcohol, instead of acting as a preservator of plants, really hastens their destruction, probably by coagulating their albumem.

Local Action.

A study of the local action of the drug shows that it causes a progressive loss of functional power in all the highly-organized tissues with which it comes in contact. Nerve-centres, peripheral nerves, muscles, both striated and unstriated, all succumb to it alike. If such contact be not continued too long, the tissue may recover, even after a total suppression of its function—a proof that the alkaloid exerts no destructive caustic influence upon the tissues, as was claimed by Van Praag. Excluding the burning pain and the anæsthesia which follow, I have never observed any action on the tongue even if the alkaloid was placed on this most sensitive organ undiluted.

In opposition to the above conclusions I must cite the statement of Van Praag (Reil's Journal of Pharmacodynamik, Hft. i. S. 33), who says that he found conia to act as a caustic when locally applied. The following experiments prove the correctness of the conclusions above given, and consequently the falsity of Van Praag's conclusion.

Exp. 5. Placed one grain of conia on my arm; in two minutes the spot was red and painful, but in five minutes on pricking the spot with a needle no pain is produced; the redness remained several hours.

Exp. 6. Exposed the gastrocnemii of the hind extremities of a frog; the right was painted with a one-grain solution of conia. In two minutes galvanism of the right gastrocnemius did not cause it to contract, while the left contracts on slight irritation. In several hours, however, the right gastrocnemius regained its power of responding to galvanic irritation.

Exp. 7. Exposed the spinal cord of a frog, and applied to it in the dorsal region a one-grain solution of conia at 11.39. 11.39$\frac{1}{4}$, voluntary movements have ceased posteriorly; irritation anteriorly causes no movements posteriorly, while irritation posteriorly, though it causes movements posteriorly, will not cause movements anteriorly. 11.39$\frac{3}{4}$, galvanization of the cord above the point where the drug was applied causes movements anteriorly but none posteriorly, while galvanization below the point of application causes movements posteriorly; thus proving that when locally applied to the spinal cord entire loss of functional power occurs at the point of application.

The drug has a similar action on the nerve trunks, for when a weak solution of the alkaloid was applied to the sciatic nerve of a mouse or frog, galvanization of the nerve above the point of application caused no contractions in the tributary muscles, but if the nerve was galvanized below the point of application contractions occurred in the tributary muscles.

The following experiments show that when locally applied to the brain of frogs conia produces immediate clonic convulsions; this is curious from the circumstance that ordinarily cerebral convulsions do not occur in batrachians.

Exp. 8. On a medium-sized frog, 5.41, a very weak solution of conia injected on the brain causes spasms immediately, 5.45, galvanization and mechanical irritation cause spasms all over the body.

Exp. 9. 6.30, a weak solution of conia was injected on the brain of a medium-sized frog, producing immediate clonic convulsions. 6.33, spasms occur with every respiratory movement.

Action on the Nervous System.

On the Brain.—It has been announced by a number of investigators that conium, like opium, produces sleep, but the drug has no such hypnotic action. Reuling and Saltzer (Deuts. Klin. 1853, No. 40) mention an experiment in which, ten minutes after the

drug was given, unconsciousness occurred, from which the animal could not be aroused. These experimenters must have been misled by the paralysis making the expression of pain absolutely impossible; in this state of affairs the eyelids are drawn together, giving still more the appearance of sleep; or from their conia being contaminated.

The state to which I have just alluded as resembling sleep is certainly not sleep, for when the abdominal aorta of a frog is tied and conia injected into the anterior part of the body, paralysis occurs anteriorly and the animal passes into this state of seeming sleep, while posteriorly, voluntary movements continue until late in the case, when paralysis of the spinal motor tract prevents all movements. Had this been sleep, voluntary movements posteriorly would have been absolutely impossible. After taking a grain and a quarter of the alkaloid I once passed into this state of seeming sleep; that this was not sleep was shown by the circumstance that consciousness was not lost, though the power over the various muscles of expression was entirely gone for the time being.

It is possible, however, that the brain becomes slightly clouded, but not to the extent to produce unconsciousness. In inducing complete repose of the muscular system, conia powerfully predisposes the brain for sleep—brings sleep within its reach, so to speak, but there leaves it. If the imagination should happen to be dull, the brain may accept the invitation, and sleep occurs.

As the convulsions of conia-poisoning are certainly cerebral, I shall now proceed to investigate this serious symptom, which really signifies that death is imminent.

Convulsions were early mentioned as symptoms of poisoning by hemlock, but the cause of these convulsions had never been determined. Christison (Trans. Roy. Soc. Ed., xiii. p. 383) imagined them to be due to a depressing action on the spinal cord, while Damourette and Pelvette (Gaz. Méd. de Paris, 37, 1870) attributed them to excitation of the cord.

It is very plain that the convulsions can be produced in but five different ways: first, they may be spinal; second, they may be due to stimulation of the peripheral ends of the motor nerves; third, they may be caused by irritation of the peripheral ends of the sensory nerves; fourth, they may be muscular; fifth, they may be cerebral.

That the convulsions of conia-poisoning are not due to irrita-

tion of either the peripheral motor or sensory nerves, nor to any direct action on the muscles, was readily proved by tying the abdominal aorta of various animals, and then injecting the drug into the anterior portion of the body, when, notwithstanding the fact that the posterior part of the body was completely cut off from the poison, convulsions occurred uniformly over the whole body.

Exp. 10. On a small male cat. Tied the left femoral artery, and, at 2.01, injected five drops of the alkaloid into the peritoneum. 12.07, repeated clonic convulsions occur over the whole animal, the left leg continuing convulsed after the others are quiet.

Exp. 11. On a very large male cat. Tied the abdominal aorta, and at 12.54, injected six drops of conia into the peritoneum. 12.57, spasms all over the body.

Exp. 12. On a young female cat. Tied the left femoral vessels, and at 5.52, injected five and a half drops of the alkaloid into the peritoneum. 5.56, convulsions, most marked in the ligatured limb.

Exp. 13. Tied the abdominal aorta of a very large mouse. 3.47½, injected one drop of conia into the anterior part of the body. 3.49, convulsions, more marked posteriorly than anteriorly.

That the convulsions are not due to irritation of the peripheral motor nerves, and that they are not muscular, was also proved by the following experiment:—

Exp. 14. Amputated a leg of a cat, and then injected an ounce of a grain solution of conia into the femoral artery. The sciatic nerve no longer caused contractions if irritated, but no spasms were produced.

The convulsions must, therefore, be either spinal or cerebral; the following experiments prove that they are not spinal:—

Exp. 15. Cut the spinal cord of a large mouse in the dorsal region. 3.47½, injected one drop of conia into the anterior portion of the body. 3.50, violent convulsions anteriorly, none at all posteriorly. 3.50½, the animal is dead.

Exp. 16. Cut the cord of a large mouse, and then injected one drop of conia into the peritoneum. In several minutes clonic convulsions occurred anteriorly, but none occurred posteriorly.

Exp. 17. On a young cat, whose cord had been cut in the dorsal region. On injecting conia, spasms had occurred in the anterior limbs, but none occurred posterior to the section.

The inevitable conclusion from these experiments is, that the

convulsions of conia-poisoning are cerebral, and not spinal, as Christison supposed.

These convulsions, according to Van Praag (loc. cit.), are always tonic in birds and fishes, but they may be either clonic or tonic in mammals; they never occur in the batrachian, except when the drug is directly applied to the brain, when they invariably are present.

Action on the Spinal Cord.—On this subject the conclusions, or, more correctly, suppositions, of different investigators are at variance. Christison (loc. cit.), Van Praag (loc. cit.), and Verigo (Schmidt's Jahrbücher, Bd. cxlix. S. 16) say that it acts forcibly as a depressant. Verigo is most positive in his declaration that all the symptoms of conia-poisoning, except paralysis, may be attributed to its depressing action on the cord. Casaubow (Practitioner, 1869) and Pelvette and Martin Damourette (loc. cit.) have come to a directly opposite conclusion, they believing that the drug is a spinal excitant. Pelvette and Damourette write: "Its excitability is but little influenced by feeble poisonous doses, since these do not produce convulsions at first, since the voluntary and reflex movements persist until the end in the frog, and since cold-blooded animals succumb without any marked change of the intellectual or instructive faculties." . . . . "With strong doses there exists an undoubted increase of excitability of the nervous centres, which is evidenced by tetanic movements and convulsive tremblings, and marked a little later by paralysis of the motor extremities. All our experiments place beyond doubt this exaltation of the spinal motor centres."

There are several points in this statement with which the writer must disagree: first, they say "the voluntary and reflex movements persist until the end in the frog, where feeble poisonous doses are given." The writer has given conia to more than a hundred frogs, thirteen of whom recovered, and, except where the principal artery of a limb was tied, in all of them complete abolition of voluntary and reflex movements occurred at some period of the poisoning. The two following are illustrative experiments:—

Exp. 18. On a medium-sized frog. 7.43, injected $\frac{1}{200}$ of a drop into the abdomen. 7.43$\frac{3}{4}$, neither voluntary nor reflex movements can be excited by the strongest current applied to the sciatic nerve.

Exp. 19. On a small frog. 2.04, injected $\frac{1}{600}$ of a grain into the abdomen. 2.08, voluntary and reflex movements still occur; 2.14, neither voluntary nor reflex movements occur, not even when the animal was irritated by galvanism. In twenty hours the animal had recovered its motive powers and was used for another experiment.

These investigators seem to imply that the convulsions are due to exaltation of the motor tract of the cord, which is far from being the case, but as they were proved to be cerebral when speaking of conia's action on the brain, nothing further need be said on the subject at present. Again, these investigators write: "With strong doses there exists an undoubted increase of the excitability of the motor centres which is evidenced by a marked paralysis of the motor extremities of nerves." How paralysis of the motor extremities of nerves proves an excitability of the motor centres is beyond the writer's comprehension, for to ordinary minds paralysis of the motor extremities of nerves is always associated with some depressing influence on the nervous centres or on the nerves themselves.

Further on in their remarks these experimenters state that the primary increase in the number of respiratory movements is due to an increased excitability of the bulbo-spinal centres, but, as the writer ascertained, that when the pneumogastrics were cut and conia given, no increase in the number of respiratory movements occurs, their view of the matter is hardly tenable.

As all the investigators have merely recorded their conclusions without the experiments on which their conclusions were based, the only way to determine the action of conia on the spinal motor tract was to go over the whole ground anew; in doing this, thirty-four experiments were made by the writer, several of which with conclusions will now be recorded.

Exp. 20. On a very large frog. A drop of acetic acid placed on its foot caused immediate reflex movements; these movements are also excited by a very weak galvanic current applied to the foot. 1.39$\frac{1}{4}$, injected one-quarter drop of conia. 1.39$\frac{1}{2}$, a drop of acetic acid placed on the foot causes reflex movements in three seconds. 1.39$\frac{3}{4}$, it takes a much stronger galvanic current to produce reflex movements than previous to the injection. 1.50$\frac{1}{2}$, the acetic acid caused movements in six seconds. 1.57, the acetic acid will no longer cause reflex movements. 2.04, it takes the strongest

galvanic current to produce reflex movements. 2.10, the strongest current no longer causes reflex movements, but the animal continues to breathe until 2.19.

This experiment, when taken in connection with thirteen others which yielded similar results, proves that early in conia-poisoning there exists no increased excitability of the cord, as is claimed by Casaubow (loc. cit.), Pelvette and Damourette (loc. cit.), for if there had been, the acetic acid would have produced reflex movements more rapidly, instead of more slowly, after injecting the conia, and it would have taken a much weaker, instead of a much stronger current to produce reflex movements. These experiments also render it probable that the action on the cord is one of depression, but this is uncertain, as the later symptoms of depression might be caused by the paralysis of the terminal extremities of the efferent nerves. To obviate this source of error, all the bloodvessels of a frog's leg were tied and the experiments repeated.

Exp. 21. On a large frog. Tied all the bloodvessels of the left posterior extremity, carefully excluding the nerves; the weakest current that would cause reflex movements in the injured limb was then determined. 3.58, injected one-eighth drop of conia. 3.59, acetic acid applied causes no reflex movements (previous to the injection it caused movements in one second). 4.01, it takes the strongest current to produce reflex movements in the ligatured limb.

Exp. 22. Tied all the bloodvessels of the left posterior extremity of a large frog, and then determined the weakest current which would cause reflex movements in the injured limb. 4.15, injected one-eighth drop of conia. 4.16¼, a much stronger current is required to produce reflex movements in the ligatured limb. 4.20, the strongest current applied to the ligatured limb will not cause reflex movements, though respiration continues and galvanization of the spinal cord causes movements in the ligatured limb.

As the ligatured limb, in the last-mentioned experiments, failed to respond to irritants after the access of the drug to the trunks and periphery of the nerves was prevented, this failure must have been due to paresis of the spinal marrow, and not to paralysis of either the afferent or efferent nerve-fibres. It is therefore proven, that, instead of there being a stage of spinal excite-

ment, there is, on the contrary, a steadily progressive stage of spinal depression.

Complete paralysis of the spinal cord is the last effect of a poisonous dose of conia, for the instant that the cord ceases to respond to galvanism, respiration ceases and death occurs.

Action on the Periphery of the Efferent Nerves.—To discuss this subject is really to discuss what has long been considered and beyond a doubt is the chief symptom of hemlock-poisoning; namely, paralysis. The cause of this paralysis has occasioned great dispute among investigators since 1835, when Christison (loc. cit.) announced that it was due to paralysis of the spinal cord; this was denied by Albers (Deuts. Klin. 1853, No. 34), who believed it to be "due to the action which conia has on the brain." Reuling and Saltzer (loc. cit.) and Van Praag (loc. cit.) agree with Christison in attributing the paralysis to the action on the spinal cord.

The first person who threw any real light on the subject was Kölliker (Virchow's Archiv, Bd. x. S. 228). In 1856, this distinguished investigator announced that the failure of motion in conia-poisoning is due to a direct action of the alkaloid upon the periphery of the efferent or motor nerves. He first experimentally proved that in frogs killed by conia the application of the galvanic current to a nerve fails to induce contractions in the tributary muscles. He then cut off the supply of blood to the hind extremities, and found that after voluntary motion had ceased anteriorly, and even after galvanic irritation of the anterior nerves had lost its influence upon the muscle directly supplied by these nerves, irritation of the same anterior nerves caused reflex contractions in the posterior extremities, thus showing that the anterior afferent nerves and the spinal cord still retained functional activity after the loss of it in all those efferent nerves reached by the poison. He then extended his experiments by severing in a frog all the tissues at the upper part of the thigh except the nerve, and found that when an animal so prepared was poisoned by conia, after the paralysis was complete in all the extremities to which the poison had access—after stimulation of the poisoned nerves failed to excite contractions in the tributary muscles—the leg which had been protected from the action of the drug, responded not only to irritation applied to its nerve, but also to stimuli placed upon distant portions of the body. After

repeating these experiments several times, he drew the conclusion previously given.

His results have been confirmed by Gultman (Reil. Mat. Med. d. Chem. Pflanzenstoffe), and by Verigo (Deuts. Zeitschr. of Arzneikunde, xxviii. 2, 1870), and by the writer in a large number of experiments. They have been denied by Dyce-Brown and Davidson (Med. Times and Gaz., July, 1870), on account of the directly opposite results which they obtained in the following experiments:—

"1. In a young cat the femoral vessels of one side were ligated under chloroform. The animal was allowed to recover from its effects, when it was found that the limb operated upon was quite as freely movable as in the uninjured leg, showing that the nervous cords had not been included with the vessels. Soon after the poison had been administered the hind legs began to move feebly, the ligatured one being equally affected with the sound one, and the two advanced *pari passu* in the general paralysis."

"2. A full-grown rabbit was treated in precisely the same way and gave identical results, the hind limb which had been operated on becoming gradually paralyzed in the same ratio as the other."

As these experiments will have to be discussed further on in this paper, I will defer my criticism until then.

Recently, upon the foundation of a single, crude, and inconclusive experiment, Harley (Old Vegetable Neurotics, p. 11) readvanced the opinion, formerly held by Albers, that conia affects chiefly the corpora striata, and the other nervous centres at the base of the brain, supposed to mediate between the will and spinal cord. The following is the experiment from which he draws his conclusions:—

"At 5.30 P. M., August 23, I injected ♏xv of the Succus conii beneath the skin of a full-grown, active, male mouse. Seven minutes afterwards he began to stumble; at the tenth minute he tumbled over several times while sitting, kangaroo fashion, upon his hind legs cleaning his face. Up to the twentieth minute the little animal continued tolerably active and self-possessed, getting up as if nothing was the matter, as often as, in sitting or walking, he happened to roll upon his side. He now gathered himself together in his usual crouching posture, and resting his nose upon the table became very still and dull, with the eyes partially closed; respirations 160—the normal rate—and regular. When aroused

he was unable to run, and on attempting to walk he rolled over on the side. Without any visible change or movement, the little animal now passed into a state of complete paralysis, in which he remained until 8.15 P. M.—two hours and three-quarters after the dose was given. During the whole of this time he lay motionless in the position in which he was placed, with his eyes nearly closed, perfectly flaccid, and exhibiting no indication of sensibility when dangled by the tail, or an ear, or a toe. As he lay upon the side the only indications of life throughout this period were the following: distinct and regular respiratory movements of the sides of the chest and abdomen, decreasing during the two hours from 160 to 135, and interrupted by one or two full swelling inspirations during the minute. On gently passing the point of the pencil along the half-closed margins of the eyelids, a sluggish contraction, so faint as to be scarcely perceptible, occurred; but on separating the lids and touching the cornea no contractile action of m. orbicularis was observable. On rolling the rump portion of the tail gently between the thumb and finger a reflex movement, consisting of a sudden jerk, of all four legs was simultaneously excited; the vibrissæ were at the same time momentarily agitated. At 8.15 P. M., the effects of the hemlock began to subside, as indicated by a little increase in the depth of the respirations, which were 135, and on irritating the tail as above mentioned, the head, body, and legs were simultaneously jerked backwards, the general movement being such as to throw the body backwards nearly an inch. The eyes were at the same time opened and the vibrissæ strongly worked. Shortly afterwards there was a slight movement in the fore paws, apparently of a voluntary nature—the first performed since the paralysis came on. But there was no further movement until 9 P. M., when on disturbing him as he lay upon his side, he struggled forwards a little, but did not succeed in getting upon his legs. This, however, was accomplished when I again disturbed him at 9.50 P. M., and he then drew himself together, opened his eyes, and began to look about him and sniff for food. Shortly afterwards he crawled a few paces, and meeting with a piece of bread and butter he licked off the butter, and then sat down on his haunches and cleaned his fore paws. At 11 P. M., he was in his usual condition (r. 140). The next day the little animal was as lively and as active as ever (r. 160), and has continued so up to the present day, August 28."

After studying this experiment again and again, one cannot help being struck with the circumstance of so eminent a physiologist and therapeutist drawing such an unwarrantable conclusion. He must have been either totally ignorant of, or he entirely ignores the investigations of Kölliker, Gultman, and Verigo. Had he attempted to galvanize one of the sciatic nerves of the paralyzed animal, he would, nay could, never have made such a mistake.

Besides this experiment the only reason that Harley gives for believing that the corpora striata are the parts affected, "is the extreme rapidity with which the paralyzing influence radiates through the body." For the same reason it might be said that the strychnia convulsions are cerebral, or that the paralysis of physostigma and atropia were due to a similar action on the corpora striata.

After studying the various papers on the subject, it will be seen that the cause of the paralysis is still somewhat undecided. It is very plain that it can be produced in four different ways: first, it may be cerebral, *i. e.*, due to a direct action on the motor centres within the brain; second, it may be due to spinal paralysis; third, it may be muscular, *i. e.*, due to a direct action on the muscles; fourth, it may be peripheral, *i. e.*, due to paralysis of the peripheral ends of the efferent or motor nerves.

That the paralysis of conia-poisoning is not muscular is proved by the fact, which has frequently been noted, and which the writer has repeatedly confirmed, that muscles taken from an animal completely paralyzed by conia—paralyzed to such an extent that galvanic irritation through the nerves fails to excite contractions — can be made to contract most energetically when the galvanic current is applied directly to the muscles. Nay, further, the irritability of the muscles through which the blood poisoned by conia has been permitted to pass is as great and as long continued as that of muscles of the same animal protected from the action of the poisoned blood by ligature of the bloodvessels.

Before discussing the question of the cause of the paralysis any further I can probably make the remainder of my experiments clearer by giving an account of several which were made to discover whether or not the application of the galvanic current to the nerves of an animal paralyzed by conia will produce contractions in the tributary muscles.

Exp. 23. On a large frog. The right sciatic nerve exposed and

galvanized; it responds to a very weak current. 3.47, injected one-twentieth of a drop of conia. 3.53, the right sciatic no longer responds to a weak current. 3.55, the strongest current applied to the sciatic nerves barely causes movements in the tributary muscles. 3.57, neither sciatic responds to the strongest current.

Exp. 24. On a medium-sized frog. 4.45, injected one-eighth drop into the abdomen. 4.55, paralysis is complete, neither of the sciatic or median nerves respond to the strongest galvanic current.

Having thus determined that galvanic irritation applied to the nerves of batrachians, paralyzed by conia, fails to induce contractions in the tributary muscles, I then proceeded to determine whether or not the same loss of irritability occurs in the nerves of mammals.

Exp. 25. On a large mouse. 1.56, injected one-half drop of conia into the peritoneum. 2.01, paralysis is complete posteriorly, and paresis anteriorly. 2.05, paralysis anterior; exposed and galvanized the sciatics without producing any contractions in the tributary muscles.

Exp. 26. On a large cat. 5.10, injected six drops of the drug into the peritoneum. 5.17, paralysis complete both anteriorly and posteriorly. 5.17½, exposed the sciatics, they will not respond to the strongest current.

The only instances in which the sciatics continued to respond after the paralysis occurred, were experiments 44 and 45, but these are only mentioned as exceptions here, as further on they are given in full with explanations.

The following experiments were made to determine whether the paralysis was cerebral or not.

Exp. 27. The spinal cord of a large mouse was cut at the tenth dorsal vertebra; irritation posterior causes reflex movements in the hind extremities. 3.47½, injected one-half drop of conia into the peritoneum. 3.50½, anterior paralysis; irritation posterior no longer causes reflex movements. The sciatics do not respond to galvanism.

Exp. 28. I repeated the last experiment, with similar results, on a medium-sized female cat. 5.52, injected four drops into the peritoneum. 6.02, paralysis anterior; reflex movements ceased posterior, and at the same time the sciatic and median nerves ceased to respond to galvanism.

These experiments show, that, if an animal is poisoned by conia after the spinal cord has been cut, galvanic irritation applied to the nerves whose communication with the brain is destroyed, like galvanic irritation applied to the nerves still in communication with the brain, fails to excite contractions in the tributary muscles. They also show that the moment that paralysis occurs in those extremities still in communication with the brain, reflex movements cease in the extremities whose communication with the brain has been destroyed.

Having thus proved that the paralysis is not cerebral, there still remain two possible causes: first, paralysis of the spinal cord; second, paralysis of the peripheral ends of the motor nerves. To determine which of these was the cause, I made a long series of experiments, a number of which will now be recorded.

Exp. 29. The left femoral artery of a cat was tied, and three drops of conia were injected into the peritoneum. In three minutes paresis occurred in the right posterior extremity, and in four minutes paresis occurred in both anterior extremities, while the left posterior extremity moved freely. The cat continued in this state for about an hour, when it commenced to recover.

Exp. 30. Into the femoral vein of the same cat six drops of conia were injected twenty-four hours after the above experiment. In ten seconds, complete paralysis except in the ligatured leg, where movements continue though they are slightly impaired.

Exp. 31. Tied the left femoral artery of a very large cat. 3.03, injected four drops of conia into the femoral vein. 3.03¼, paralysis of all the limbs except the ligatured one, where movements continue though they are slightly impaired. 3.04, galvanization of the right sciatic nerve causes no contractions, but galvanization of the left sciatic causes contractions in its tributary muscles.

Exps. 32, 33, 34, and 35. Repeated the last experiment on four cats, with similar results.

Results similar to these were obtained when frogs were experimented with, as will be shown by the following experiment.

Exp. 36. Tied the abdominal aorta of a medium-sized frog. 4.13, injected one-fourth drop of conia into the anterior portion of the body. 4.17½, paralysis is complete anteriorly, but voluntary and reflex movements persist posteriorly. 4.20, the sciatics respond to a weak current, but the median nerves will not respond to the strongest current.

I tied the abdominal aorta and then gave conia to twenty-seven other frogs, and always obtained results similar to those obtained in Experiment 36. In the two following experiments the sciatic nerve of one side was cut, while the main artery of the other hind leg was tied; so soon as anterior paralysis occurred the peripheral end of the cut sciatic ceased to respond when galvanism was applied, while on the ligatured side the sciatic when irritated caused contractions until long after death.

Exp. 37. Tied the left popliteal artery and cut the right sciatic nerve of a frog. Both sciatics respond equally well to galvanism. 3.09, injected one-quarter drop of conia beneath skin of the back. 3.17, paralysis complete, excepting the left leg. 3.18, galvanized the peripheral end of the right sciatic without producing any contractions, while galvanism applied to the left sciatic causes contractions in its tributary muscles.

Exp. 38. Another frog was treated in exactly the same manner and gave identical results. After paralysis had occurred in the two uninjured extremities, galvanism was applied to the cut sciatic with no effect, and then to the sciatic isolated from the poison by ligature of the main artery, producing contractions in its tributary muscles.

In the two following experiments I separated in frogs all the tissues at the upper part of one of the thighs except the nerve; conia was then given, and after paralysis had occurred this nerve continued to respond to irritants, while the nerve on the opposite side refused to conduct impressions.

Exp. 39. Separated in a frog all the tissues at the upper part of the left thigh, except the nerve. 2.13, poisoned the animal with one-twentieth drop of conia. 2.21, paralysis complete in all portions of the body to which the poison has access; after galvanic stimulation of the right sciatic and of the median nerves failed to excite contractions in the tributary muscles, the left leg responded not only to irritation applied to its nerve, but also to galvanic stimulation applied to other portions of the body.

Exp. 40. Repeated the last experiment with similar results.

These experiments show that when the direct access of the poison to a limb is prevented, that limb never becomes paralyzed; thus proving that the paralysis must be due to the action on the efferent or motor nerves.

If any further proof be wanted of this action of conia on the

periphery of the efferent nerves, I think that the following experiment (one of four, all giving similar results) must put an end to all doubts.

Exp. 41. Killed a cat with chloroform, and then cut off both posterior extremities at the hip-joint. Into the left femoral artery I injected a one-grain solution of conia, while into the right ordinary water was injected. In thirty seconds the application of the galvanic current to the left sciatic nerve causes no response, while its application to the right sciatic caused contractions in its tributary muscles.

The same results were obtained in the following experiments in which conia and strychnia were given simultaneously.

Exp. 42. Injected conia and strychnia into the abdomen of a frog from whose posterior extremities direct access of the poison had been cut off by tying the abdominal aorta; by their conjoint action they produced a commingling of paralysis in all other parts of the body with violent tetanic spasms in the protected limbs. This commingling would have been impossible if the paralysis was spinal or cerebral, and can only be explained on the supposition that conia paralyzes all the motor nerves with which it comes in contact.

Exp. 43. Severed in a frog all the tissues at the upper part of the right thigh except the nerve, and then injected one-twentieth drop of conia with one-sixtieth grain of strychina. In seven minutes paralysis in all other parts of the body with the peculiar strychnia convulsions in the right leg.

The two experiments of Dyce-Brown and Davidson (previously given in full), seemingly prove that the paralysis is either spinal or cerebral and not peripheral ; there can, however, be but little importance attached to them, as the effect of galvanism on the spine and on the nerve of the ligatured limb was not observed. In a single experiment I obtained results similar to those obtained by these experimenters, but the reason for this was soon made clear by finding an anomaly in the external iliac artery ; this vessel, instead of being solely continuous with the femoral, gave rise to a large branch which passed directly to the back of the leg, becoming popliteal. I have observed the same anomaly in five dogs, seven cats, and two mice, and in frogs this anomalous distribution occurs so often that it is probably the rule with them and not the exception. In several dissections of various animals I

have seen the internal iliac pass down the back of the leg while there was a very small femoral in front. It is very probable, had a dissection been made, that the unusual results obtained by Brown and Davidson would have been explained by some anomalous distribution of the arteries.

The two following experiments I am unable to explain except on the supposition that conia has a double action on the motor nervous system; a paralyzing action on the peripheral ends of the efferent or motor nerves, and a depressing action on the motor tract of the spinal cord; that in almost all cases the former occurs first and predominates, the paralysis of the spinal cord not occurring until the period of death, yet in a few instances the former does not occur at all and the latter becomes more marked than usual. The experiments to which I allude are the following:—

Exp. 44. Tied the left femoral artery of a young cat. 12.05, injected five drops of conia into the peritoneum. 12.17, paralysis all over the body, not even excepting the ligatured limb; the application of the galvanic current to either sciatic causes as strong contractions in the tributary muscles, as it did previous to injecting the conia (showing that the peripheral ends of the motor nerves were not paralyzed). I then opened the spine and galvanized the cord without producing any movements in the extremities.

Exp. 45. Tied the left external iliac of a young cat. 5.10, injected three-quarters of a drop of conia into the femoral vein. 5.25, no paralysis. 5.25½, injected one drop into the femoral vein. 5.36½, no paralysis. 5.37½, injected two drops. 5.51, slight paresis, equally marked in the ligatured as in the uninjured extremities. 5.52, injected two drops. 5.55, complete paralysis all over the body, not excepting the ligatured limb. Galvanization of either sciatic causes strong contractions in the tributary muscles, while galvanization of the spine produces no effect.

Action on the Periphery of the Afferent Nerves.—Except the loss of irritability of the eyes the sensory nervous system has always been supposed to remain unaffected in conia-poisoning. In some of the earlier experiments made by the writer evidences were seen which threw doubts on this supposition, but, later, when the following experiments were made, especially to determine this point, these doubts became certainties.

Exp. 46. Tied the abdominal aorta and left axillary artery of a

medium-sized frog. 2.49, injected one-eighth drop of conia into the abdomen. 2.58, the right fore leg is paralyzed, the rest of the extremities move freely. One pole of a galvanic battery on the spinal cord and the other on the left fore leg causes reflex movements in the hind legs, while with the same pole on the spine and the other on the right fore leg, the same current being applied, no reflex movements occurred.

Exps. 47 and 48. Repeated the last experiment with similar results.

These experiments not only prove that sensation is impaired, but, as this impairment did not occur in the ligatured anterior extremity and was very manifest in the uninjured extremity, it must have been due to the action of the drug on the periphery of the afferent or sensory nerves.

In opposition to these conclusions could be cited all investigators on hemlock since the time of Christison, but as I have yet to find the first paper in which efforts have been made to prove that loss of sensation does not occur, but little importance can be attached to such assertions.

Action on the Circulatory System. On the Pulse.—As is shown by the following experiments, conia, in ordinary therapeutic doses, causes an increase in the number of heart beats, with a subsequent decrease, but in these doses the disease never goes below the original number of beats.

No. of experim't.	Animal.	Time.	Dose.	Pulse.
49	Man	.....	.....	72
.....	.....	10.47	$\frac{1}{16}$ gr.	....
.....	.....	.50	.....	80
.....	.....	.51	.....	90
.....	.....	$\frac{1}{2}$	.....	90
.....	.....	.53	.....	80
.....	.....	.55	.....	80
.....	.....	11.00	.....	76
.....	.....	.01	.....	76
.....	.....	.03	.....	76
.....	.....	.07	.....	72
.....	.....	.09	.....	72
.....	.....	.11	.....	78
.....	.....	.15	.....	74
.....	.....	.21	.....	74
.....	.....	.27	.....	72
.....	.....	.50	.....	72

No. of experim't.	Animal.	Time.	Dose.	Pulse.
50	Man	.....	.....	72
.....	.....	1.39	$\frac{1}{12}$ gr.	....
.....	.....	.40	.....	93
.....	.....	.52	.....	92
.....	.....	.56	.....	94
.....	.....	.57	.....	104
.....	.....	.58	.....	100
.....	.....	2.01	.....	98
.....	.....	.04	.....	100
.....	.....	.11	.....	90
.....	.....	.15	.....	88
.....	.....	.18	.....	88
.....	.....	.26	.....	86
.....	.....	.29	.....	80
.....	.....	.34	.....	80
.....	.....	.36	.....	86
.....	.....	.39	.....	84
.....	.....	.43	.....	84
.....	.....	.44	.....	82
.....	.....	.54	.....	72
.....	.....	.56	.....	72
51	Man	.....	.....	76
.....	.....	3.14	$\frac{1}{9}$ gr.	....
.....	.....	.16	.....	84
.....	.....	.18	.....	86
.....	.....	.25	.....	88
.....	.....	.32	.....	84
.....	.....	.35	.....	88
.....	.....	.36	.....	93
.....	.....	.38	.....	97
.....	.....	.46	.....	88
.....	.....	.49	.....	92
.....	.....	.58	.....	100
.....	.....	4.00	.....	92
.....	.....	.30	.....	76
.....	.....	5.05	.....	76
52	Man	.....	.....	84–88
.....	.....	1.56	$\frac{1}{7}$ gr.	....
.....	.....	2.00	.....	104
.....	.....	.01	.....	102
.....	.....	.02	.....	110
.....	.....	.03	.....	104
.....	.....	.05	.....	100
.....	.....	.06	.....	96
.....	.....	.11	.....	112
.....	.....	.12	.....	100
.....	.....	.14	.....	98
.....	.....	.17	.....	96
.....	.....	.20	.....	96
.....	.....	.21	.....	94
.....	.....	.24	.....	90
.....	.....	.26	.....	91
.....	.....	.28	.....	92
.....	.....	.30	.....	94

No. of experim't.	Animal.	Time.	Dose.	Pulse.
52	Man	2.37	.....	92
.....	.....	.39	.....	92
.....	.....	.53	.....	88
.....	.....	.54	.....	86
.....	.....	.58	.....	84
.....	.....	3.00	.....	88
.....	.....	.24	.....	86
53	Man	.....	.....	81
.....	.....	1.10	$\frac{1}{6}$ gr.	....
.....	.....	.11	.....	81
.....	.....	.17	.....	87
.....	.....	.28	.....	86
.....	.....	.30	.....	88
.....	.....	.35	.....	91
.....	.....	.40	.....	92
.....	.....	.47	.....	90
.....	.....	.49	.....	90
.....	.....	2.00	.....	88
.....	.....	.04	.....	82
.....	.....	.28	.....	82
.....	.....	.35	.....	82

In poisonous, and even in full therapeutic doses, the subsequent decrease in the number of pulsations goes far below the normal number, as will be seen in the following experiments:—

No. of experim't.	Animal.	Time.	Dose.	Pulse.
54	Man	.....	.....	80
.....	.....	2.25	$\frac{1}{3}$ gr.	.....
.....	.....	.27	.....	80
.....	.....	.29	.....	80
.....	.....	.31	.....	80
.....	.....	.34	.....	80
.....	.....	.37	.....	80
.....	.....	.40	.....	90
.....	.....	.42	.....	89
.....	.....	.43	.....	84
.....	.....	.55	.....	84
.....	.....	.58	.....	82
.....	.....	3.00	.....	80
.....	.....	.02	.....	80
.....	.....	.03	.....	88
.....	.....	.04	.....	87
.....	.....	.07	.....	89
.....	.....	.09	.....	72
.....	.....	.11	.....	72
.....	.....	.13	.....	72
.....	.....	.16	.....	76
.....	.....	.17	.....	74

No. of experim't.	Animal.	Time.	Dose.	Pulse.
54	Man	3.18	.....	72
.....	.....	.19	.....	66
.....	.....	.20	.....	72
.....	.....	.21	.....	72
.....	.....	.25	.....	72
.....	.....	.54	.....	62
.....	.....	4.00	.....	72
.....	.....	.30	.....	80
.....	.....	.45	.....	80
55	Mouse	.....	.....	120
.....	.....	12.45	1 gtt.	.....
.....	.....	.46	.....	140
.....	.....	.48	.....	120
.....	.....	.50	.....	99
.....	.....	.55	.....	72
.....	.....	1.01	.....	00
56	Cat	.....	.....	230
.....	.....	5.10	$\frac{3}{4}$ gtt.	.....
.....	.....	.13	.....	300 (estimated)
.....	.....	.16	.....	300 "
.....	.....	.21	.....	252 "
.....	.....	.26	1 gtt.	.....
.....	.....	.32	.....	312 (estimated)
.....	.....	.35	.....	240
.....	.....	.38	2 gtt.	.....
.....	.....	.39	.....	252
.....	.....	.40	.....	214 (estimated)
.....	.....	.53	3 gtt.	.....
.....	.....	.55	.....	(probably) 400
.....	.....	.58	.....	252
.....	.....	.59	.....	180
.....	.....	6.01	.....	120
57	Frog	.....	.....	72
.....	.....	9.03	$\frac{1}{40}$ gtt.	.....
.....	.....	.04½	.....	78
.....	.....	.06	.....	72
.....	.....	.07	.....	68
.....	.....	.14	.....	42

To prove whether or not the primary increase was due to some action on the pneumogastric centres, I made the following experiments:—

No. of experiment.	Animal.	Time.	Dose.	Pulse	Remarks.
58	Mouse	....	....	....	Cut both vagi.
....	....	....	....	250	....
....	....	1.56	$\frac{1}{2}$ gtt.	....	....
....	....	.57	....	250	....
....	....	2.00	....	250	....
....	....	.02	....	250	....
....	....	.03	....	250	....
....	....	.05	....	250	....
....	....	.08	....	225	....
....	....	.10	....	225	....
....	....	.15	....	225	....
....	....	.22	....	70	Resp's ceased.
....	....	.24$\frac{1}{2}$	....	24	....
....	....	.25	....	1	....

As no increase occurred after the pneumogastrics were cut, the increase in the number of pulsations in the other experiments must have been due to a depressing action on the pneumogastric centres. The subsequent diminution in the number of pulsations can readily be explained by the occurrence of paresis of the vaso-motor nerves, this latter being due to commencing paralysis of the cord.

Arterial Pressure.—Conia causes the column of mercury in the cardiometer to be decidedly lowered at first, but very soon the mercury again rises to far above its original height. The following experiment illustrates this:—

Exp. 59. On a large cat. Normal pressure, $7\frac{1}{2}$ to 8 cent. met. 2.07, injected one drop of conia into the femoral vein. 2.08, arterial pressure, 7 to $7\frac{1}{2}$. 2.09, arterial pressure, 8 to $8\frac{1}{2}$. 2.10, pressure, $8\frac{1}{2}$ to 9. 2.11, pressure, 10 to 11.

Action on the Respiratory System.—The first effect of a poisonous dose of conia is to cause an increase in the number of respiratory movements; this is followed, sooner or later, by a diminution, and ultimately, if the dose be sufficiently large, by their complete cessation.

No. of experiment.	Animal.	Time.	Dose.	Respirations per minute.	Remarks.
60	Frog	....	....	156	....
....	....	1.00	$\frac{1}{200}$ gtt.	....	....
....	....	.01$\frac{1}{2}$	....	252	....
....	....	.02	....	190	Paralysis.
....	....	.05	....	9	....
....	....	.07	....	0	Spinal paralysis.

No. of experiment.	Animal.	Time.	Dose.	Respirations per minute.	Remarks.
61	Frog	....	....	84	....
....	....	1.20	$\frac{1}{400}$ gtt.	....	....
....	....	$\frac{1}{2}$	....	126	....
....	....	.22	....	90	....
....	....	.24	....	78	....
....	....	.26	....	0	Spinal paralysis.
62	Cat	....	....	21	....
....	....	12.45	3 gtt.	....	....
....	....	$\frac{1}{2}$	....	61	....
....	....	.46	....	36	....
....	....	.48	....	26	Paralysis.
....	....	.57	....	8	....
....	....	1.02	....	0	Spinal paralysis.
63	Cat	....	....	112	....
....	....	5.10	$\frac{3}{4}$ gtt.	....	....
....	....	.14	....	126	....
....	....	.17	....	140	....
....	....	.21	....	132	....
....	....	.25	....	150	....
....	....	$\frac{1}{2}$	1 gtt.	....	....
....	....	.28	....	148	....
....	....	.29	....	150	....
....	....	.35	....	108	....
....	....	.37$\frac{1}{2}$	2 gtt.	....	....
....	....	.38	....	228	....
....	....	.40	....	224	....
....	....	.42	....	168	....
....	....	.51	....	108	Convulsions.
....	....	.54	....	104	Convulsions.
....	....	.58	....	64	Paralysis.
....	....	.59	.. .	30	....
....	....	6.00	....	8	....
....	....	.01	....	2	....
....	....	.02	....	0	Spinal paralysis.
64	Frog	....	....	150	....
....	....	5.20$\frac{1}{2}$	$\frac{1}{200}$ gtt.	....	....
....	....	.21	....	160	....
....	....	.24	....	120	....
....	....	.27	....	16	Paralysis.
....	....	.28	....	0	Spinal paralysis.
65	Mouse	....	....	100	Vagi uncut.
....	....	4.57$\frac{1}{4}$	1 gtt.	....	....
....	....	$\frac{1}{2}$	....	110	....
....	....	.58$\frac{1}{2}$	....	120	....
....	....	5.04	....	100	....
....	....	.06	....	50	Paralysis.
....	....	.06$\frac{1}{2}$	....	20	....
....	....	.08	....	16	....
....	....	$\frac{1}{4}$	....	0	Spinal paralysis.

Pelvette and Damourette (loc. cit.) supposed that the acceleration of the respiratory movements was due to spinal excitation, in which supposition they were undoubtedly wrong, as it was shown when speaking of conia's action on the spinal cord that no excitation occurs. As the following experiment proves that the primary acceleration of the respiratory movements does not occur when both pneumogastrics have previously been divided, the acceleration is probably due to paresis of the pneumogastric centres.

No. of experiment.	Animal.	Time.	Dose.	Respirations per minute.	Remarks.
66	Mouse	....	....	....	Cut both vagi.
....	....	....	....	120	....
....	....	1.56	½ gtt.	....	....
....	....	.57	....	110	....
....	....	2.00	....	108	....
....	....	.01	....	108	....
....	....	.03	....	112	....
....	....	.05	....	104	....
....	....	.07	....	104	....
....	....	.10	....	104	....
....	....	.12	½ gtt.	....	....
....	....	.15	....	100	....
....	....	.20	....	0	....

Kölliker (loc. cit.) supposed that the diminution and the subsequent complete failure in the respiratory movements were due to the action on the peripheral ends of the efferent nerves causing paralysis of the muscles concerned in respiration, but as I prove in the following experiments that the respiratory movements continue long after the occurrence of paresis, or even paralysis, his explanation will have to be abandoned.

Exp. 67. On a large frog. 3.09, injected one-quarter drop of conia into the abdomen. 3.14, paresis over the whole body; respiration continues. 3.17, the paralysis is now complete, but respiration continued until 3.22.

Exp. 68. 5.19, injected one-half drop of conia into the abdomen of a frog. 5.24, complete paralysis, but the respiratory movements continue until 5.31.

Exp. 69. On a young cat. 12.52, injected three drops of conia into the peritoneum. 12.57, the paralysis is complete, but the respirations continue until 1.20.

Exp. 70. 2.12, injected one drop of conia into the peritoneum of a mouse. 2.15½, the paralysis is complete, but the respiratory movements continue until 2.20.

The following experiments show that the paralysis of the spinal cord and the cessation of respiratory movements occur at the same time, rendering it very probable that the latter is an effect of the former.

Exp. 71. Tied the abdominal aorta of a frog. 10.36, injected one-hundredth of a drop of conia into the abdomen. 10.39¾, the paralysis is complete anteriorly; respiration still continues, and galvanization of the spinal cord causes movements in the ligatured limbs. 10.41, respiration ceased; galvanization of the cord produces no movements.

Exp. 72. On a medium-sized cat. 1.00, injected three drops of conia into the peritoneum after tying the left femoral artery. 1.08, paralysis, but respiration continues. 1.30, respiration ceased, and galvanization of the cord causes no response.

Exp. 73. Tied the abdominal aorta of a mouse. 2.02, injected one drop of conia into the peritoneum. 2.10, respirations ceased; galvanization of the cord causes no response.

Gastro-Intestinal Action.

In ordinary medicinal doses no gastro-intestinal symptoms occur in man; in experiments upon myself grain doses were unable to produce attempts at vomiting, or even anorexia. Out of one hundred and forty-eight conia experiments made by the writer, but three cases of vomiting occurred, and these were in dogs, who, as is well known, vomit very readily.

Exp. 74. On a young dog. 8.10, gave him one-half grain of conia by the mouth; in three minutes he vomited. On the following day an injection of one-half grain into the peritoneum caused vomiting in a very short time.

Exps. 75 and 76. Vomiting occurred when conia was injected into the femoral vein.

In these experiments vomiting took place when conia was introduced through other channels than by the mouth and stomach, and they, therefore, prove that the gastro-intestinal irritation is not due to any local action on the alimentary canal, as is claimed

by Harley (loc. cit. p. 82): it must be the result, as in the case of opium, of a specific action on the gastro-intestinal apparatus.

These symptoms are not exclusively canine, but they also occur in man, as attempts at vomiting are recorded by Bennet (Ed. Journ. Med. Sci. 1845) in case of poisoning by hemlock leaves, and Schroff (Vierteljahrschr. f. Praktische Heilkunde, 1855), in his experiments with conia on the human subject, records one case in which there was actual vomiting.

Action on the Glandular System.

One of the first effects of a very large therapeutic dose of conia, in about one-half of the writer's experiments, was to increase the secretion of the salivary glands. This increase is not due to any local action, as it occurs when the drug is injected into a vein or into the peritoneum.

As regards the drug's effect on the urinary secretion, my experiments compel me to endorse the conclusion of Verigo (loc. cit.), who asserts that "conia has no influence on the quantity or quality of the urine." Casanbau (loc. cit.), however, believes that in the beginning the secretion of the kidneys, like that of the salivary glands, is increased. Probably this investigator was misled through the fact that the animals voided their urine soon after a large dose of the drug was administered, but this urination is due to the spasmodic contractions of the muscular fibres of the bladder, which almost always occurs.

I have never observed any action on the skin, as evinced by either an increase or a decrease in the amount of perspiration, and, as other investigators are silent on this point, it is very probable that its function remains unaffected.

Conia's action on the biliary secretion has not yet been determined, but the circumstance, first noticed by Nega (Zeitschr. f. Klin. Med. Breslau; 1850, 1), and confirmed by Van Praag (loc. cit.), that after death from conia-poisoning, the gall-bladder is always found distended with bile, renders it probable that it increases the biliary secretion. In all the *post-mortem* examinations made by the writer on animals poisoned by conia, this distension of the gall-bladder was invariably present.

Action on the Muscular System.

The voluntary muscles escape unscathed in conia-poisoning, they continuing to respond to galvanism for a long time after death. The contractility of the muscles, however, may be destroyed by soaking in a very concentrated solution of the alkaloid, but before such an effect can be produced in life, the animal will have perished.

On the non-striated muscular fibres the action of the drug is more pronounced; Geiger (Mag. f. Pharm. xxxv. S. 72 u. 256), states that it produces irritation of the involuntary muscular fibres of the diaphragm and alimentary canal. In the experiments made by the writer, contractions of the muscular fibres of the intestinal canal and bladder were observed.

Action on the Pupil.

Dr. Hoppe (Die Nervenwirkung d. Heilmittel, Leipsic, Hft. 1), made a number of experiments to determine this action of the drug, and in conclusion says: In the beginning the pupil is contracted, but later it becomes very much dilated. His conclusion has been confirmed by Pelvette and Demourette (loc. cit.), who attribute the contraction to augmentation of the excitability of the spinal cord.

The conclusions drawn by the writer from a number of experiments made especially to determine this point, are as follows: When conia is introduced hypodermically, or given by the stomach, the pupil never contracts, but sooner or later it always dilates, this dilatation being due to the paresis of the peripheral extremities of the ciliary branches of the motor-oculi nerve, no longer enabling the sphincter of the iris to counteract the radiating fibres supplied by filaments from the more slowly paralyzing sympathetic nerve. When locally applied conia at first contracts and then dilates the pupil, the dilatation occurring from the absorption of the drug. As the contraction did not occur when conia was introduced hypodermically or given by the stomach, it must be due to its local irritant action, and not to augmentation of the excitability of the spinal cord.

Action on Temperature.

All investigators of the action of conia have thus far agreed on one point, to almost totally ignore this action of the drug. One copying from the other, all saying that the temperature is lowered, and, as far as I am aware, until this investigation, no one even imagined that conia was so peculiar as to be one of three drugs (atropia, woorara,(?) and conia) that cause a decided increase in the temperature of the animals poisoned. This increase occurs not only from poisonous doses, but also when full therapeutic doses are administered. This increase in temparature lasts from three-quarters of an hour to an hour and a half, when the temperature gradually becomes normal.

No. of experim't.	Animal.	Time.	Dose.	Temperature.
77	Cat	.....	.....	$99\frac{3}{4}$°
.....	.....	5.10	$\frac{3}{4}$ gtt.	.....
.....	.....	.15	.....	101
.....	.....	.17	.....	$100\frac{1}{2}$
.....	.....	.23	.....	100
78	Man	.....	.....	$97\frac{1}{2}$
.....	.....	$3.14\frac{1}{2}$	$\frac{1}{9}$ gr.	.....
.....	.....	.21	.....	$97\frac{1}{2}$
.....	.....	.30	.....	$98\frac{3}{4}$
.....	.....	.45	.....	$98\frac{3}{4}$
.....	.....	4.00	.....	$98\frac{1}{2}$
.....	.....	.36	.....	$98\frac{1}{2}$
.....	.....	5.19	.....	$97\frac{1}{2}$
79	Man	.....	.....	97
.....	.....	1.56	$\frac{1}{7}$ gr.	.....
.....	.....	.59	.....	97
.....	.....	2.09	.....	$98\frac{1}{2}$
.....	.....	.17	.....	$98\frac{3}{4}$
.....	.....	.19	.....	99
.....	.....	.22	.....	$99\frac{1}{5}$
.....	.....	.24	.....	$99\frac{1}{4}$
.....	.....	.28	.....	$99\frac{1}{3}$
.....	.....	.32	.....	$99\frac{1}{2}$
.....	.....	.30	.....	$99\frac{1}{2}$
.....	.....	3.24	.....	$97\frac{1}{2}$
80	Man	.....	.....	97
.....	.....	1.10	$\frac{1}{6}$ gr.	.....
.....	.....	.24	.....	$98\frac{1}{2}$
.....	.....	.33	.....	99
.....	.....	.50	.....	$98\frac{1}{2}$
.....	.....	2.28	.....	$97\frac{1}{2}$

No. of experim't.	Animal.	Time.	Dose.	Temperature.
81	Man	.....	.....	$96\frac{1}{3}^{\circ}$
.....	.....	4.40	$\frac{1}{6}$ gr.	.....
.....	.....	.54	.....	$97\frac{1}{2}$
.....	.....	5.20	.....	$97\frac{1}{2}$
.....	.....	.35	.....	$97\frac{1}{2}$
.....	.....	.56	.....	$98\frac{1}{3}$
.....	.....	6.25	.....	$97\frac{1}{2}$
.....	.....	.55	.....	$96\frac{1}{2}$
82	Man	.....	.....	$98\frac{1}{2}$
.....	.....	1.39	$\frac{1}{12}$ gr.	.....
.....	.....	.44	.....	$98\frac{1}{2}$
.....	.....	2.07	.....	99
.....	.....	.15	.....	99
.....	.....	.31	.....	$98\frac{1}{2}$

Action on the Sexual Organs.

The genital depression attributed to conium by the ancients, modern investigators have been unable to discover. The ancients believed, that not only does it repress sexual desire, but that it actually caused an atrophy of the testes and mammæ, which latter, of course, implies atrophy of the ovaries also. The falsity of this belief was shown in several cases of chorea, occurring in girls about the age of puberty, in whom menstruation came on while the patients were under the physiological effects of conia. That it has no effect on the mammary secretion of cats is proved by the following experiment.

Exp. 83. A four-year-old cat was delivered of kittens on July 20th. On the evening of the same day she was given one drop of conia by the stomach, and on the next morning another drop was given, with the following result: great difficulty in moving and respiring, without any apparent effect on the mammary secretion, the kittens sucking freely. On the morning of the 22d, another drop was given, and, until the 29th, the animal was given a drop daily without any noticeable effect on the quantity or quality of the milk; the kittens continuing very healthy, but in all of them some of the physiological effects of the poison being at times manifest.

In order to determine, whether or not conia, in non-poisonous doses, has the power to arrest or depress natural sexual desire, an experiment was made on a large tom cat, who is in the habit of

enlivening our dreams by midnight concerts in the backyard. He was given one-twentieth of a grain of conia on four consecutive nights. Finding that this dose produced no effect, on the fifth night I gave him two drops hypodermically, yet that night, though very much under the influence of the drug, he, after many failures, managed to creep to his trysting place and commenced his regular nocturnal music. This experiment proves beyond a doubt that conia has no power to arrest or depress natural sexual desire; but while this is the case in the normal condition, morbid states are said to be much influenced by the drug. In proof of this, Dr. Harley (loc. cit. p. 51) writes: "In those states of exhaustion and irritability which arise from self-abuse; and in those cases of erotic tendency that arise from some obscure irritation of the lumbar portion of the cord, I have never known conium to fail to give relief." In my opinion, however, this relief is better explained by referring it to the depressant action which the drug has on the spinal cord, than to any possible action on the sexual organs.

Absorption and Elimination.

That conia is absorbed is beyond question, as it has been found by Orfila in the spleen, kidneys, and lungs of poisoned animals. Absorption occurs without regard to the manner in which the drug is introduced into the system, but when the drug is placed on the whole skin in small quantities, absorption does not take place. That this must be due to its great volatility is shown by the following experiment.

Exp. 85. Placed thirteen very small frogs in a weak solution of conia at 4.31; took them out in one-half minute. 4.35, four of the frogs are paralyzed. At 4.37, three more were paralyzed, and by 4.40, all were paralyzed.

Absorption must have taken place through the skin of these animals, as the solution merely reached up to their abdomen.

Conia undergoes no change in the system, although Harley says it does, because he failed to find it in the urine of poisoned animals; yet it is eliminated by the kidneys, in whose secretion Zaleski and Draggendorf (H. C. Wood's Therapeutics) have found abundance of it in the first twelve hours of the poisoning, and traces of it for two days and a half.

That it is not necessary for conia to be changed in the system

in order to produce its most marked effect, that on the periphery of the efferent or motor nerves, was proved by the following experiment.

Exp. 86. Cut off both hind legs of a cat previously killed with chloroform; both sciatics respond equally well to galvanism. Into the left femoral artery a one-grain solution of conia, while into the right an equal quantity of water was injected. In thirty seconds the application of the galvanic current to the left sciatic nerve causes no response, while its application to the right sciatic causes contraction in its tributary muscles.

The following physiological test proves, conclusively, that conia is eliminated by the urine.

Exp. 87. Placed two small frogs in the urine of a coniinized animal; in forty seconds they were both taken out completely paralyzed.

Exp. 88. Placed two small frogs in the urine of another coniinized animal, and obtained results similar to those obtained in the last experiment.

As the conclusions at which I have arrived are scattered throughout the essay, it has been thought proper at this point to present a concise summary of the conclusions previously given.

I. Conia, instead of being poisonous to plants, as has heretofore been supposed, really acts as a preservative; the alcoholic extract of hemlock, however (probably through some impurities which it contains, but, above all, not through the action of conia, which it rarely contains), acts poisonously on plants.

II. When locally applied, conia produces a progressive loss of functional power in every highly organized tissue with which it comes in contact. If such contact be not continued too long, the tissue may recover, even after a total suppression of its function.

III. In inducing complete repose of the muscular system, conia powerfully predisposes to sleep, but it is not a hypnotic in the sense that opium is.

IV. The convulsions produced by a poisonous dose of hemlock are cerebral, and not spinal, as has heretofore been imagined.

V. Conia produces a double effect on the motor-nervous system, —a paralyzing effect on the periphery of the efferent or motor nerves, and a depression of the motor tracts of the spinal cord. In almost all the experiments the former occurred first and pre-

dominated, the paralysis of the cord not occurring until the period of death, but in two experiments the peripheral paralysis failed to occur, while the spinal paralysis was manifest much earlier.

VI. The increase in the number of heart beats which occurs early in conia-poisoning, is due to paresis of the pneumogastrics; the subsequent decrease is due to paresis of the vaso-motor nerves, this paresis being due to commencing paralysis of the motor tract of the spinal cord.

VII. The primary acceleration in the respiratory movements is also due to pneumogastric paresis, while their diminution, which soon occurs, is caused by, and proceeds *pari passu* with the paresis of the spinal motor tract.

VIII. The salivary secretion is the only secretion markedly increased by a poisonous dose of conia.

IX. The voluntary muscles escape unscathed in conia-poisoning; their contractility, however, may be destroyed by soaking in a concentrated solution of the alkaloid. Contractions of the non-striated muscular fibres of the alimentary canal and bladder are caused by poisonous doses.

X. Contraction of the pupil only occurs when the drug is directly applied to the eyeball; it is then due to irritation. The dilatation of the pupil occurring after the absorption of conia is due to paresis of the peripheral extremities of the ciliary branches of motor-oculi nerves, no longer enabling the sphincter of the iris to counteract the radiating fibres supplied by the more slowly paralyzing sympathetic nerve.

XI. Conia, unlike almost every other drug of the materia medica, and contrary to the statement found in all works on therapeutics, causes a decided increase in temperature.

XII. The genital depression attributed to conium by the ancients must have depended entirely on their imaginations, and not on atrophy of the testes and mammæ.

XIII. Conia is absorbed and is eliminated unchanged by the kidneys.